REMARKS

Claims 1-31 were originally pending. Applicants previously canceled the original claims and presented the elected claims as new claims 32-37 and added claims 38-46. Accordingly, claims 32-46 were pending for purposes of the instant action. All claims stand rejected.

As shown above, claim 32 has been amended. Applicants respectfully submit that no new matter has been added by the above amendments to the claims.

Reconsideration of these currently pending claims is respectfully requested.

I. Claim Rejections under 35 USC 112

Claims 37-46 stand rejected under 35 USC 112, first paragraph, as being non-enabled for a metalloproteinase-related disease or disorder. Applicants respectfully traverse.

The fundamental finding that MMP-9 is inhibited by the BAPTA diesters in combination with the vast amount of established literature that demonstrate the linkage between MMP-9 activity and certain diseases and disorders enable a range of indications which is broader than the actual tested model systems and includes enablement for metalloproteinase-related diseases or disorders as claimed. The pre-clinical, in-vitro data presented in the subject application clearly support the claims as currently recited, and would enable a person of ordinary skill in the art to practice the invention without undue experimentation.

Applicants maintain that it is not necessary to conduct and present the results of clinical trials in order to claim a therapeutic activity as the Office Action appears to suggest. It is common knowledge in the art of drug development that a molecule that targets a key element which is essential for or contributes to the manifestation of a disease or disorder, is a potential candidate for serving as a medicament for treating such medical condition.

In the interest of advancing the prosecution of the subject application to allowance, applicants have further amended the claims to specifically recite cancer and inflammation disorders as the particular metalloproteinase-related disease or disorder treated.

Support for cancer treatment may be found in Examples 3 and 4, where DP-BAPTA compounds were tested, respectively, on rat and human glioma cell lines and were shown to reduce both basal and TNF-alpha-induced MMP-9 activities. It is well established that elevated expression of MMP-9 is associated with tumor proliferation and in particular with pathogenic mechanisms in cancer such as invasion, metastasis and angiogenesis. Therefore, MMPs, and in particular MMP-9, may be a rational target useful in the treatment of many types of cancer, including those types which are invasive, i.e., infiltrative (such as gliomas) or highly metastatic.

Support for the inflammation indication may be found in Example 3, which shows that diesters of BAPTA inhibited both basal and TNF-alpha-induced MMP activity. As tumor necrosis factor alpha (TNF-alpha) is a pro-inflammatory cytokine and as MMP-9 is highly expressed at sites of inflammation and contributes to the pathogenesis of inflammatory diseases, applicants believe the recitation of treating inflammation is clearly supported.

Example 8 demonstrates the effect of several DP-BAPTA molecules on the levels of TNF-alpha released in response to stimulation of primary glial cells with lipopolysaccharide (LPS). It was shown that the DP-BAPTA molecules were effective in reducing the induction of TNF-alpha release in primary glial cells. It is important to note that in this particular case the TNF-alpha release was induced by LPS, which is a bacterial component. In Example 9 it was also suggested that DP-BAPTAs may inhibit TNF-alpha release from macrophages.

In view of the above, applicants respectfully submit that, regardless of the cause of inflammation, any inflammatory disease or disorder which is mediated by the cytokine TNF-alpha and involves MMP-9 may benefit from treatment with diesters of BAPTA of the present invention.

Finally, it should be pointed out that the Examiner's statement on page 3 of the instant Action that "for a compound or genus to be effective against inflammation generally: is contrary to medical science" is not entirely accurate. In fact, there are drugs, most notably, steroids, for example, that can and are successfully used for a wide range, if not almost all kinds of inflammations.

II. Rejection of the Claims under 35 USC 102(b) and 35 USC 103(a)

Claims 32-39 and 44-46 stand rejected under 35 USC 102(b) as being anticipated by or, in the alternative, under 35 USC 103(a) as being unpatentable over Kozak, et al. (WO 99/16741).

The subject claims have been amended to specifically recite treatment of "metalloproteinase (MMP)-related disease or disorder selected from cancer and TNF-alpha-mediated inflammation." Accordingly, applicants believe the subject claims are distinguished from the cited reference which the Office Action admits does not recite specific MMP-related conditions. Because the cited reference does not describe each and every element of the current claims, the cited reference cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection under 35 102(b) is respectfully requested.

Regarding the obviousness issue, it is noted that the cited Kozak reference is directed to lipophilic diesters of chelating agents for the treatment of conditions and diseases related to elevated levels of divalent metal ions, and in particular, the treatment of conditions and diseases related to elevated levels of intracellular Ca^{++} ions.

By contrast, the subject application claims the use of these lipophilic diesters of the chelating agent (DP-BAPTAs) for treating conditions and diseases associated with metalloproteinase (MMP) activity, and more specifically, treating cancer or certain inflammatory conditions. Thus, the claimed invention concerns the newly discovered inhibition of MMP activity, and in particular the inhibition of MMP-9 activity, by the DP-BAPTAs. This aspect of the subject invention is disclosed for the very first time in the subject application and was not taught or suggested in the prior art – and particularly

not taught or suggested by the disclosure of the cited Kozak refernce. The method of treating MMP-related conditions or diseases, as currently claimed, is completely unexpected from the elevated divalent metal ion treatment described in the Kozak reference.

Conditions or diseases not related to MMP, such as those relating to divalent metal ion elevation as described in Kozak, are not within the scope of the claims as currently presented. All MMP-related conditions or disorders (e.g., ischemia, Alzheimer's disease, and Parkinson's disease, and the like) that may overlap with diseases or disorders described in the Kozak reference are not recited, or were removed from the claims. The claimed invention, as expressly recited, is unobvious in view of the Kozak disclosure.

Reconsideration and withdrawal of the rejection under 35 USC 103(a) is respectfully requested.

III. CONCLUSION

A timely and favorable action in the subject application is respectfully urged.

Respectfully submitted,
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